Throwing it in reverse: An update on reversal of oral factor Xa inhibitors

In recent years, the use of oral Factor Xa (FXa) inhibitors such as rivaroxaban and apixaban, have seen more extensive utilization for stroke prevention in non-valvular atrial fibrillation and the prevention/treatment of venous thromboembolisms [1,2]. Some studies have shown a similar bleed risk between FXa inhibitors and warfarin while other studies demonstrated a decreased risk for a bleed with FXa inhibitors. Despite a possible decreased risk, the paucity of data available for treating an acute major bleed due to FXa inhibitors has led some clinicians to shy away from their use. Since major bleeding events like intracranial hemorrhages (ICH) and hemorrhagic shock secondary to gastrointestinal bleeds (GIB) are associated with high morbidity and mortality, many clinicians are unsure of how to proceed with managing these patients.

Andexanet alfa is a novel antidote recently approved by the FDA for reversal of apixaban and rivaroxaban [3]. Prior to the release of andexanet alfa, the standard of care for reversal of oral FXa inhibitor associated major bleeds was the utilization of four factor prothrombin complex concentrate (PCC) as endorsed by multiple guidelines; however, with an FDA approved reversal agent available clinicians must now weigh the pros and cons of each agent given the available evidence (Table 1) [4,5].

PCC does not act as a reversal agent but rather increases prothrombotic activity by providing excess clotting factors. With the available evidence, PCC has shown to achieve hemostasis anywhere from 66 to 95% of the time; however, it is important to note this data is based off lower quality evidence and has not been confirmed in a randomized controlled trial with a comparator group. A common concern for providers is that giving excess clotting factors it places patients at risk for development of thromboembolic events; however, the majority of safety data with PCC has shown risk of thromboembolic events to be <10% [5-7]. Additionally, there is currently no consensus on the appropriate dosing regimen to utilize for PCC ranging anywhere from 25 to 50 units/kg. Furthermore, there are various PCC formulations that have been evaluated for FXa inhibitor reversal which potentially introduces bias [5-7]. One of the remaining questions with PCC is the ethical and legal issue of continuing to utilize it for FXa inhibitor reversal given the fact there is a FDA approved reversal agent. To answer some of these questions, a randomized controlled trial comparing andexanet alfa versus PCC will soon begin recruiting for enrollment.

Andexanet alfa works as a decoy for the FXa inhibitor to bind to irreversibly. The recently completed ANDEXA-4 trial, which was a prospective, open-label, single group study, found that patients achieved good or excellent hemostasis in 82% of subjects [13-15]. There was an overall 10% thromboembolic event rate, reduction in anti-Xa activity by 92%, and 14% mortality associated with andexanet alfa use. Some concerns were raised during and after the trial however, primarily as it pertained to the overall acuity of the patients enrolled, lack of correlation between anti-Xa activity reduction and hemostasis, and complicated dosing scheme. Another major concern with the use of andexanet alfa is its price point. The low dose and high dose regimens cost approximately $25,000–$50,000, respectively. In comparison, a max dose regimen of PCC would be approximately $8000–$10,000 depending on the final dosage. Lastly, there were concerns on the actual logistics of getting the medication to the patient secondary to the prolonged administration times noted in the ANDEXA-4 trial; however, it must be noted that some of this would be expected secondary to the determination of high vs. low dose regimen arms. Ultimately, andex-

Table 1
Studies evaluating FXa inhibitor reversal [6-9,10-12,14,15].

Author	Study design	Anticoagulant	No. of patients	Hemostatic efficacy	Thrombotic events	Mortality/failure	Type of bleed included total N (%)	Dose	Exclusion criteria/limitations
Tao et al	Retrospective Chart Review	Rivaroxaban (49%) Apixaban (51%)	43	40/43 (93%)	1 (2%) (Upper ext. DVT)	2/43 deaths, 1/43 (failed required surgery) (7%)	- ICH non-traumatic: 9 (21%) - ICH traumatic: 7 (16.3%) - GI: 17 (39.5%) -Trauma: 5 (11.6%) -Other: 5 (11.6%)	4F-PCC 25–50 IU/kg	- Patients received 4F-PCC for purposes other than reversing factor Xa inhibitors - Patients under 18 years of age
Schulman et al	Multicenter Prospective Cohort Study	Rivaroxaban (56%) Apixaban (44%)	66	Good 43 Moderate 13 Poor/None 10 85% Overall	5 (8%) Major events	9 deaths (14%) by 30 days	- ICH: 36 (54.6%) - GI: 16 (24.2%) - Trauma: 25 (37.9%) - Intra-spinal: 2 ((3%) - Retroperitoneal 3 (4.6%) - Intramuscular 2 (3%) - Other: 7 (10.6%)	4F-PCC fixed dose of 2000 units	- DNR order - Patients without an evident source of bleeding - Patients with ACS or ischemic stroke within past 30 days

Majeed et al	Multicenter Prospective Trial	Rivaroxaban (53%) Apixaban (47%)	84	69.1%	3 (4%) (2 strokes, 1 suspected PE)	27 deaths (32%) by 30 days	- ICH 59 (70.2%) - GI 13 (15.5%) - Visceral 5 (6%) - GU 4 (4.7%) - Musculoskeletal 3 (3.6%)	≤65 kg received 1500 IU 4F-PCC >65 kg received 2000 IU 4F-PCC	- DNR order - Patients without an evident source of bleeding - Preoperative reversal - Patients with ACS or ischemic stroke within past 30 days
Santibanez et al	Retrospective Study	Rivaroxaban (66%) Apixaban (34%)	38	78.9% (81.3% in major bleeds and 66.7% for emergent surgery)	3 (7.1%)	Overall Hospital mortality (26.9%) (Didn't report separate mortality rate for oral Factor Xa Inhibitors)	- 2 groups (major bleeding and emergent surgery)	4F-PCC range of 1500–2500 IU Average dose in each group approximately 25 units/kg.	
Dager WE et al	Retrospective Analysis	Rivaroxaban (58%) Apixaban (42%)	48	95.8% Follow-up did not reveal any clinically concerning active bleeding or notable.	8%	9 deaths (18.8%) by 30 days	- ICH (58.3%)	Low dose FEIBA dosing strategy (<20 units/kg) or moderate dosing strategy of (25 units/kg)	- Authors concluded that 6 of the 9 deaths most likely would not have been enrolled in previous reversal trials secondary to the sizes and severity of bleeds
Allsion et al	Retrospective Observational Study	Rivaroxaban (82%) Apixaban (18%)	31	84% but 4 (12.9%) patients did require additional doses of PCC and 11 (35.5%) patients did receive fresh frozen plasma	No events reported	2 deaths (5%)	- ICH: 8 (24.2%) - SAH: 9 (27.2%) - TBI: 13 (39.4%) - GI: 1 (3%) - Hematoma with active extravasation 1 (3%) - Intra-abdominal 1 (3%)	4F-PCC 35 units/kg	- Exclusion criteria included pregnant and incarcerated patients
Gerner et al	Retrospective Cohort Study	Rivaroxaban (75%) Apixaban (14%)	146	66.7%	No events reported	19.9% at discharge	ICH: 100% ICH volume, median cm^3: 28.5	4F-PCC 25–50 units/kg	Results confounded by blood pressure management
Andexanet Alfa	Multicenter Prospective Open Label Single-group	Rivaroxaban (36%) Apixaban (55%) Enoxaparin (6%) Edoxaban (3%)	352	82% (With respect to clinical outcomes) - Rivaroxaban group factor Xa activity fell by 89% - Apixaban group factor Xa activity fell by 93%	10%	14% by 30 days	- ICH 64% - GI bleeding 26% - Other 10%	Refer to table1 for dosing regimen Andexanet Alfa	- Extensive exclusion criteria - Surgery within <12 h after presentation (except minimally invasive surgery or procedure) - Intracranial hemorrhage with GCS < 7 - Estimated intracerebral hematoma volume > 60 mL - Expected survival <1 month - Major thrombotic event within 2 weeks before enrollment - One of the following within 7 days before screening: vitamin K antagonist, dabigatran, PCC, or whole blood or plasma

anet alfa is currently the only FDA approved agent for the reversal of FXa inhibitors and should at minimum facilitate discussions amongst facilities on whether or not to add to their institutional formulary.

The American College of Cardiology has issued a guidance sheet, which now recommends andexanet alfa as first line therapy for the reversal of apixaban and rivaroxaban. Absent from their formal recommendation is edoxaban, but this is secondary to the low volume of subjects who were enrolled in the ANDEXA-4 trial who were receiving edoxaban. The Society of Critical Care Medicine/Neurocritical Care Society guidelines have not updated since andexanet alfa's approval but do have a section that mentions if available to consider andexanet alfa use. Also, it is important to highlight the heterogeneity between the majority of the studies evaluating PCC or andexanet alfa as it relates to how they measured hemostasis and safety parameters. In addition, each study that has evaluated FXa inhibitor reversal has not had a comparator group, which can lead to major confounders and bias. While an FDA approved agent for FXa inhibitor reversal was certainly welcomed there remains ambiguity as to which agent should be utilized first, as salvage therapy, or even combination.

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Antibiotic selection and isolate susceptibility profile in patients who failed ciprofloxacin or TMP-SMX for pyelonephritis

To the Editor

We read with interest the retrospective study by Vogler and Pavich assessing treatment failure in women diagnosed with uncomplicated pyelonephritis who were discharged from the emergency department on an oral fluoroquinolone (FQ) or trimethoprim-sulfamethoxazole (TMP-SMX) versus an oral cephalosporin. The primary endpoint of treatment failure occurred in 0% of patients receiving an oral cephalosporin and 23% of patients receiving FQ or TMP-SMX [1].

The authors stated in their discussion that the high resistance rates reported in their institution's weighted antibiogram may have predisposed the FQ/TMP-SMX group to higher treatment failure. However, according to their secondary objective analysis, only 3% of organisms isolated were resistant to ciprofloxacin. In contrast, 23% of organisms isolated were resistant to TMP-SMX. It would be of interest to know which antibiotic the ten patients who failed treatment received, either ciprofloxacin or TMP-SMX, and the isolates' susceptibility profile. The current presentation of data with TMP-SMX and ciprofloxacin being analyzed together, despite the strikingly different resistance rates, raises the question of whether the authors' conclusion that "treatment with oral cephalosporins may be a more appropriate therapy for uncomplicated pyelonephritis versus fluoroquinolones or trimethoprim-sulfamethoxazole" is appropriate without addressing if antibiotic resistance, particularly to TMP-SMX, was the main contributor to treatment failure in the FQ/TMP-SMX group. The manner in which the patient outcomes data were analyzed and presented leaves this as an unanswered question.

Moreover, we appreciate the authors' concern with prescribing empiric ciprofloxacin and TMP-SMX since their reported weighted-average antibiogram data demonstrated *Escherichia coli* non-susceptibility rates of 23% and 24% to ciprofloxacin and TMP-SMX, respectively. Further validating this concern is the Infectious Diseases Society of America guideline recommendation of using an initial one-time parenteral dose of ceftriaxone or consolidated 24-hour dose of an aminoglycoside for acute pyelonephritis when the prevalence of FQ resistance exceeds 10%, or if the uropathogen susceptibility to TMP-SMX is unknown [2]. It was noted in the arti-